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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,543	01/17/2002	David E. Lam		7769

25225 7590 11/29/2006

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,543	LAM ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,14-16,18-20,22-32 and 34-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-9, 14-16, 18-20, 22-32, 34-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 4-9, 14-16, 18-20, 22-32, 34-59 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 6-26-06, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Examiner has withdrawn the rejection under 35 USC 102(e) in view of the persuasive arguments provides by the applicant.

Drawings

Examiner notes that applicants have filed a color photograph. Color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-9, 14-16, 18-20, 22-32, 34-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-2, 4-9, 14-16, 18-20, 22-32, 34-59 are drawn to a) an isolated, synthetic or recombinant polypeptide having endoglucanase activity or b) an isolated, synthetic or recombinant nucleic acid molecule encoding a polypeptide having endoglucanase activity. Applicant has amended the claim by introducing the word "synthetic" in the claims. However, a perusal of the specification indicates that applicants have no support for "synthetic" which now constitutes a "new matter". Therefore claims 1-2, 4-9, 14-16, 18-20, 22-32, 34-59 are rejected for introducing "new matter" into the claims.

Claims 1-2, 4-9, 14-16, 24-30, 32, 38-53, 55-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an endoglucanase having the amino acid sequence SEQ ID NO:46 or a polypeptide having 95% amino acid sequence identity to SEQ ID NO:46 and having endoglucanase activity, encoded by a polynucleotide having the nucleotide sequence SEQ ID NO:45 or 95%, 97% nucleotide sequence identity to SEQ ID NO:45, vectors and host cells comprising said polynucleotide, does not reasonably provide enablement for any such polypeptide that has 90% sequence identity to SEQ ID NO:46 or polypeptides comprising 30 or 50 amino acids of a polypeptide that is 90% or 95% or 97%

identical to SEQ ID NO:46 or cellulase polypeptides comprising 30 or 50 consecutive amino acids of SEQ ID NO:46 or a polypeptide encoded by a polynucleotide having a nucleotide sequence which is either 90%, identical to SEQ ID NO:45 or a probe comprising 15, 25, 35, or 50 nucleotides of a polynucleotide having a sequence that is at least 90%, 95% or 97% identical to SEQ ID NO:45, vectors and host cells comprising said polynucleotides and method of making said polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-2, 4-9, 14-16, 24-30, 32, 38-53, 55-59 are so broad as to encompass any variants of SEQ ID NO:46 or any endoglucanase polypeptide that has 90%, sequence identity with SEQ ID NO:46 or polypeptides comprising 30 or 50 amino acids of a polypeptide that is 90% or 95% identical to SEQ ID NO:46 or cellulase polypeptides comprising 30 or 50 consecutive amino acids of SEQ ID NO:46 or any variants of SEQ ID NO:45 or any polynucleotide having a nucleotide sequence which 90%, identical to SEQ ID NO:45 or a probe comprising15, 25, 35, or 50 nucleotides of a polynucleotide having a sequence that is at least

90% identical to SEQ ID NO:45, vectors and host cells comprising said polynucleotides and method of making said polypeptides.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides and polynucleotides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single endoglucanase. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides and polynucleotides. The specification is limited to teaching the use of SEQ ID NO: 45 and 46 as a endoglucanase but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any endoglucanase polypeptide and polynucleotide encoding the same because the specification does not establish: (A) regions of the protein structure which may be modified without affecting its activity; (B) the general tolerance of endoglucanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including endoglucanases with an enormous number of amino acid modifications to SEQ ID NOS:46. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptide having endoglucanase activity and the polynucleotides encoding the same is unpredictable and the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection and continue to argue at length that the specification enables those skilled in the art at the time the invention was made to identify and make and use a genus of polypeptides having endoglucanase or cellulase activity and the nucleic acids that encode them to practice the claimed invention.

Applicants maintain that the specification enabled the skilled artisan at the time of the invention to identify, and make and use, the genus of polypeptides and refer again to Dr. Short's declaration, regarding making mutants or variants using a given sequence of a endoglucanase.

Examiner has indeed considered Mr. Short's Declaration and the previous arguments. In essence, Applicants argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because the specification teaches the complete sequence of the enzyme, and protocols for testing enzymatic activity, and methods for producing variants of a disclosed sequence are within the skill of the ordinary artisan. Applicants argue that while the number of samples needed to be screened may be high, the procedures are routine and yield successful results. Applicant also argues that screening large numbers of composition --as long as the screening is routine--, is irrelevant to enablement and reiterates a court decision handed down. Examiner respectfully disagrees with all the above arguments.

Referring to the Office's argument of lack of guidance to make the mutants and variants, applicant continues to maintain that the specification and level of knowledge to the skilled artisan was more than enough guidance to satisfy enablement requirement.

Applicant continues the same previous argument that the skilled artisan using the teaching of the specification had sufficient (reasonable) guidance as to what base or amino acid substitutions could have been made to make the genus of endoglucanases of the invention (e.g., what amino acid substitutions could have been made to make the genus of glycosidase enzymes of the invention), that information was, inter alia, readily available in the form of endoglucanase sequences known in the art at the time of the invention. Applicant maintains that a routine, simple sequence alignment comparison of known glycosidase sequences would have identified regions of identity and dissimilarity to provide guidance to the skilled artisan as to which sequences could be changed, or not changed, to generate structural and/or functional variations of an exemplary endoglucanase. With such information, applicant argues, that if one skilled in the art desired some structural guidance as to what amino acid substitutions could be made to make the genus of endoglucanase of the invention, such guidance could be found both in the specification and the state of the art at the time of the invention. Examiner respectfully disagrees with such a line of argument. This is because, irrespective of whatever guidance provided in the specification or in the art, one of ordinary skill in the art will be subject to undue experimentation in order to arrive at active polypeptides having glycosidase activity at said per cent homologies. Although the claims are not limited to variants having only a single amino acid substitution, in order to generate only *single* amino acid variant of SEQ ID NO:46, one must make 19^{319} just for *single amino acid variants*. This number was determined by recognizing that SEQ ID NO:46 is 319 amino acids in length. Because there are 19 other possible naturally occurring L-amino acids that can replace each amino acid of SEQ ID NO:2, the number of possible variations is 19^n, where n = number of amino acids in a polypeptide. Thus, for only *single* amino acid

substitutions, the number of variants is 19^{360} and the number becomes seemingly infinite when one considers that the claims broadly encompass simultaneous alteration of substitution, addition, deletion, and/or insertion of up to 31 amino acids (for 90% sequence identity) in a polypeptide that is 360 amino acids in length. Based on this rough approximation, *the number of allowed permutations is astounding.* While methods to produce variants of a known sequence, e.g., site-specific mutagenesis and random mutagenesis, are well-known to the skilled artisan, producing variants having glycosidase activity requires that one of skill in the art know or be provided with guidance for the selection of which of the *at least* 19^{319} variants has the desired activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the at least 19^{319} possible variants. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants as is the case for the claims limited to 95% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the claims to 90% or less identity (for example, making a variant glycosidase comprising any 30 amino acids of SEQ ID NO:46) would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. Hence the above rejection is maintained.

Claims 27-30, 56-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of polypeptides having endoglucanase activity and comprising 30 or 50 amino acids of a polypeptide that has 90% or 95% sequence identity to SEQ ID NO:46 or 30 to 50 amino acids of SEQ ID NO:46. The specification does not contain any disclosure of the structure of all such sequences included in the claimed genera. The genus of polypeptides claimed is a large variable genus with the potentiality of having different structures. Therefore, many structurally distinct polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus (i.e., that of SEQ ID NO:46) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by sequence or a recitation of structural features common to members of the genus, **which features constitute a substantial portion of the genus**. The recited structural feature of the genus (i.e., polypeptides having endoglucanase activity and comprising 30 or 50 amino acids of a polypeptide that has 90% or 95% sequence identity to SEQ ID NO:46 or polypeptides comprising 30 to 50 amino acids of SEQ ID NO:46) does not constitute a substantial portion of the genus as the remainder of the structure of such polypeptide having endoglucanase activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one

skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the above rejection, applicants have traversed. Again applicants argue at length that claims are indeed described. With respect to pending claims 27-30 directed to polypeptides having endoglucanase or cellulase activity comprising at least 30 or 50 amino acid residues of a polypeptide having at least 90% or 95% sequence identity to SEQ ID NO:46 or at least 30 or 50 amino acids of SEQ ID NO:46, applicants argue that the instant amendment addresses this issue by narrowing the scope of the claimed genera of polypeptides i.e., the limitation of 90% and 95% sequence identity. Examiner respectfully disagrees that amending the claims to recite "90% or 95%" does not in any way remedy the written description problem. Claims are still drawn to polypeptides comprising just 30 or 50 amino acids of said sequences and the structure of remaining portion of such polypeptides remains unknown.
Applicants also argue that the Office implies that claimed fragments of claims 27 to 30 may encompass non-active polypeptides and that the claims are expressly limited only to polypeptides having endoglucanase or cellulase activity. Here again, Examiner completely disagrees with such an argument. First of all the Office has not implied that claims are drawn to non-active polypeptides at all. Second, applicant is not claiming fragments of SEQ ID NO:46. Applicant is claiming a polypeptide comprising a fragment of SEQ ID NO:46 without providing

the full structure of such a polypeptide. Applicant should keep in mind that the claim in question are NOT limited to fragments of SEQ ID NO:46.

Next, applicant argues the Office implies that the claimed genera of polypeptides are "short on structure and recite only function" but in fact, the claims expressly set forth the structural parameters of all, or the active portion, of the claimed polypeptides - for example, in one aspect of claims 27 or 28, the invention encompasses a genus of polypeptides having endoglucanase or cellulase activity consisting of 30 or 50 amino acid residues of a polypeptide having 90% sequence identity SEQ ID NO:46. Examiner respectfully disagrees that the languages of rejected claims provide structural features of claimed polypeptides. The most structural aspect provided by the applicant in the claim is that the polypeptide comprises 30 to 50 amino acids of a given sequence. That is a partial structure. Applicant's argument that providing percent sequence identity of the polypeptide some how provides more structural information of the claimed polypeptides is highly misplaced. New claims 57-59 also suffer from the same problem. Even in these claims providing percent sequence homologies does not remedy the written description issue. Therefore the above rejection is maintained.

Claims 40-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules comprising 15, 25, 35, or 50 contiguous nucleotides of a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO:45.

The specification does not contain any disclosure of the function of all DNA sequences that are encompassed by the claim. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of encoding many different proteins. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the above rejection, applicants maintain the same above arguments as that used for the above rejection for polypeptides. Examiner refers the applicant to his arguments above.

Conclusion

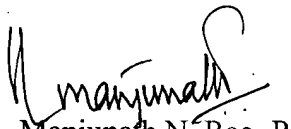
None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

November 13, 2006